Original Article

Maternal Inhibin A and Activin A Levels as Markers of a Viable Trophoblast in Incomplete and Complete Miscarriage

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Abstract

Background: From early gestation the human trophoblast secretes large amounts of inhibin A and activin A, and their measurement provides a value for predicting the outcome in women who become pregnant after assisted reproductive techniques. **Objective:** The aim of this study was to look at the potential function of maternal serum inhibin A and activin A as markers of viable trophoblast in women who miscarry, and to compare their value to β-hCG. **Materials and Methods:** A case-control study that was conducted in the Department of Obstetrics and Gynecology over a period from February 1 till October 1, 2019. It included 91 women with singleton pregnancy proved by a positive pregnancy test, serum β-hCG measurement, and ultrasound examination. They were divided into three groups: complete group included 23 pregnant women diagnosed as complete miscarriage, incomplete group included 23 pregnant women diagnosed as incomplete miscarriage, and control group included 45 pregnant women with viable pregnancy, no history vaginal bleeding. Test for inhibin A level, for activin A level, for β-hCG level, and transvaginal and/transabdominal ultrasound were done. **Results:** Means of β-hCG, activin A, and inhibin A levels were significantly lower in patients of complete group than that in incomplete and control groups. β-hCG < 8750 mIU/mL, activin A < 822 pg/mL, and inhibin A < 104.81 pg/mL were found to be predictive for the occurrence of complete miscarriage. Mean of β-hCG, activin A, and inhibin A levels were significantly lower ($P < 0.05$) in complete group than that other groups both in early and late 1st trimester miscarriage. **Conclusion:** There is a possible role of inhibin A in signaling early pregnancy problems especially if combined with β-hCG. Activin A level is considered as promising biomarker in combination with inhibin A in determining the reminisce of viable from non-viable trophoblastic tissue.

Keywords: Activin A, inhibin A, Iraq, Miscarriage, pregnancy, β-hCG

Introduction

Miscarriage is the spontaneous loss of a pregnancy before 24 weeks of gestation, or the evacuation of a baby weighing less than 500 g, that is, before the fetus is normally viable outside the uterus.[1] Miscarriages are most common in the first trimester of pregnancy. A miscarriage occurs in 8%–15% of clinically identified pregnancies. However, roughly 30% of all pregnancies end in a miscarriage, according to estimates. As a result, miscarriage is the most prevalent pregnancy complication.[2,3] Chromosomal abnormalities are the most common cause of spontaneous pregnancy loss in the first trimester.[4] Maternal and paternal factors are more important in pregnancy losses that are determined to have a normal chromosomal makeup, referred to as euploid abortions.[5] The trophoblastic shell is thinner and fractured in two-thirds of cases, and cytotrophoblast invasion to the terminals of the spiral arteries is diminished. This causes premature initiation of maternal circulation throughout the placenta and incomplete plugging during early pregnancy.[6] The increased input of maternal blood into the intervillous area has both a direct mechanical and an indirect oxidative stress effect on the villous tissue, contributing to cellular malfunction and/or damage. The correlation of in vivo and in vitro data suggests that placental tissue oxidative

Access this article online

Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_692_23

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Submission: 06-Jun-2023 **Accepted:** 11-Sep-2023 **Published:** 30-Sep-2025

How to cite this article: Abdulrazaq SK, Rifat AG. Maternal inhibin A and activin A levels as markers of a viable trophoblast in incomplete and complete miscarriage. Med J Babylon 2025;22:692-7.

stress is a common pathophysiological mechanism for the various causes of miscarriage.[7] Inhibin is a disulfide-linked glycoprotein dimer hormone that belongs to the transforming growth factor-β (TGF-β) superfamily and consists of the -subunit and one of several -subunits. Inhibin A (α-βA) and inhibin B (α-βB) are two inhibins.[8] Inhibin A is primarily synthesized and secreted by placental syncytiotrophoblasts during pregnancy, and it plays a role in the regulation of various hormones in the placental local regulatory axis, as well as endometrial decidualization, embryo implantation, trophoblast proliferation, and differentiation. It has an impact on the onset, progression, and continuation of pregnancy. As a result, inhibin A may have an impact on fetal growth and pregnancy outcomes. Inhibin A levels peaked between 8 and 10 weeks of pregnancy, remained relatively consistent between 14 and 30 weeks, climbed steadily from the third trimester to full term, and peaked at birth.[9] Activin A is a TGF-β superfamily dimeric growth factor that plays a vital role in endometrial differentiation, trophoblastic invasion, and embryo implantation.[10] Recently, researchers looked at the involvement of inhibin and activin in recurrent miscarriage and discovered that inhibin A was a particular preclinical marker of early pregnancy loss. A strong link has been discovered between serum inhibin levels and β-hCG levels.[11] The aim of this study was to look at the potential function of maternal serum inhibin A and activin A as markers of viable trophoblast in women who miscarry, and to compare their value to β-hCG as a quick and practical diagnostic of viable placentation in early pregnancy.

Materials and Methods

Study design, setting, and time

This was a case control study that was conducted in the Department of Obstetrics and Gynecology at Azadi Teaching Hospital, Kirkuk over a period of eight months from February 1 till October 1, 2019.

Study population and sample size

The study included initially 96 women with singleton pregnancy proved by a positive pregnancy test, serum β-hCG measurement, and ultrasound (U/S) examination, who attended the obstetrics ward or outpatient clinic of the hospital. All patients were informed about the nature of the study and verbal consent was obtained from them. Five participants showed invalid or missing activin A and inhibin A marker results, so the total number of participants included in the analysis was 91. All pregnant women were between 5 and 12 weeks' gestation assessed by menstrual dates and confirmed by U/S scan performed in the preceding 1 week before sample collection. Women with twin or multiple pregnancy, ectopic pregnancy, diabetes mellitus, hypertension, other medical illness, fetal anomaly and infection, hydatidiform mole, women taking exogenous progesterone, conceived after ovarian stimulation, with history of previous miscarriage as they may need further investigation, with history of ovarian surgery or significant uterine abnormality, women taking drugs, and women who are smoking were excluded from this study. Women included in the study were divided into three groups[11]:

- **Complete group:** Included 23 pregnant women who presented with vaginal bleeding for at least 12 h and diagnosed as complete miscarriage by U/S examination which showed an empty uterus with a history of the passage of the products of conception.
- **Incomplete group:** Included 23 pregnant women who presented with vaginal bleeding for at least 12 h and diagnosed as incomplete miscarriage by U/S examination that showing a retained piece of conception and no fetus.
- **Control group:** Included 45 pregnant women with viable pregnancy, no history vaginal bleeding.

A questionnaire was applied to all enrolled pregnant women to collect the needed information. Detailed history was taken including age, obstetrical history (parity, last menstrual cycle, and gestational age), gynecological history including subfertility or previous induction of ovulation and previous gynecological surgeries, chronic medical diseases, and drug history. They were subject to complete physical examination including general examination, vital signs and abdominal examination. Body mass index (BMI) was calculated by weight in (kilograms) divided by the square of height in (meters). Pelvic examination for all patients for evaluation of the uterine size and cervical dilatation. Investigations: In addition to routine investigations which include (complete blood count, blood group and rhesus group, blood sugar, etc.), following investigations were done: Test for inhibin A level, for activin A level, for β-hCG level, and transvaginal and/transabdominal U/S. Women in the incomplete group were treated conservatively, medically, or surgically, depending on the clinician's decision. Women in the control group must be followed up on for the next 24 weeks to ensure that their pregnancy is still continuing on.

The inhibin A and activin A kits principles were based on sandwich enzyme-linked immune-sorbent assay technology. Then centrifugation was done at 5000 rpm for 5 min. Then the serum was stored at –80°C until the analysis time. The assay of β-hCG was electronic – linked fluorescent assay that was performed in an automated instrument. The detection range for inhibin A is 15.625-1000 pg/mL, for activin A is 62.5-4000 pg/mL according to manufacturer's information and for β-hCG is 2-1500 mlU/mL.

Statistical analysis

Statistical Package for Social Sciences version 25 was used to analyze the data (SPSS, IBM company,

Chicago, IL, USA). The information is displayed in the form of a mean, standard deviation, and ranges. Frequencies and percentages are used to present categorical data. The continuous variables were compared using a two-tailed independent *t* test. The prediction of biomarkers as indicative of abortion was done using receiver operating characteristic curve analysis. A *P*value of less than 0.05 was deemed significant reference.[12]

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with pregnant patients with verbal and analytical approval before sample was taken. The study protocol and the pregnant women information and consent form were reviewed and approved by a local ethics committee according to the document number 1 (including the number and the date in February 1, 2019).

Results

No significant difference was found among level activin, inhibin A level, and β-hCG Level among the studied group the two groups.

In this study, participants' age was ranging from 19 to 42 years with a mean of 28.17 ± 7.17 years. There were no statistically significant differences ($P \geq 0.05$) between study groups in age, BMI, GA and parity. Means of *β*-hCG, Activin A, and Inhibin A levels were significantly different in patients of complete, incomplete and control groups (P value = 0.001) as shown in Table 1.

In this study, participants' age was ranging from 19 to 42 years with a mean of 28.17 ± 7.17 years. There were no statistically significant differences ($P \geq 0.05$) between study groups in age, BMI, GA, and parity. Means of β-hCG, activin A, and inhibin A levels were significantly lower in patients of complete group than that in incomplete and control groups as shown in Table 1.

No significant difference was found among level activin, inhibin A level, and β-hCG level among the studied group the two groups.

Furthermore, there was no statistically significant relationship found among the level A activin, inhibin A level, and β-hCG level between the complete and incomplete groups with P value = 0.001.

Post hoc tests (LSD) showed that means of β-hCG, activin A, and inhibin A levels were significantly lower in patients with complete miscarriage than that in controls. Means of β-hCG and inhibin A levels were significantly lower in patients with incomplete miscarriage than that in controls. Means of activin A, and inhibin A levels were significantly lower in patients with incomplete miscarriage than that in controls ($P < 0.05$). No significant difference ($P = 0.055$) detected in mean of β-hCG level between patients with complete miscarriage and patients with incomplete miscarriage and no significant difference ($P = 0.064$) in mean of activin A level between patients with incomplete miscarriage and that in controls as shown in Table 2.

ROC curve analysis was constructed for β-hCG, activin A, and inhibin A markers as predictors for the occurrence of complete miscarriage. As shown in Table 3 and Figures 1–3, the cut-off point of β-hCG was 8750 mIU/mL, activin A was 822 pg/mL, and inhibin A was 104.81 pg/mL. Thus, β-hCG < 8750 mIU/mL, activin A < 822 pg/mL, and inhibin A < 104.81 pg/mL were found to be predictive for the occurrence of complete miscarriage as a large significant area under the curve (AUC= 95.5%, 84%, and 89.9% respectively) indicating significant association between lower levels of β-hCG, activin A, and inhibin A markers and possibility of complete miscarriage. β-hCG marker concentration was 95.7% sensitive, 88.9% specific, and 92.3% accurate, serum activin A marker concentration was 78.3% sensitive, 86.8% specific, and

Table 1: Comparison between study groups in certain parameters

Variable	Study group			*P*-value
	Complete Mean ± SD	Incomplete Mean ± SD	Control Mean ± SD	
Maternal age (year)	27.9 ± 6.3	28.5 ± 8.2	28.2 ± 7.4	**0.966**
BMI (kg/m^2)	26.2 ± 3.8	25.7 ± 4.3	25.0 ± 3.4	**0.479**
Parity	1.86 ± 1.6	1.39 ± 1.3	1.51 ± 1.4	**0.393**
GA (week)	7.86 ± 1.8	8.65 ± 1.9	8.0 ± 1.6	**0.261**
β-hCG level (mIU/mL)	1446.2 ± 519.8	4626.3 ± 2601.0	13301.2 ± 7623.1	**0.001**
Activin A level (pg/mL)	720.4 ± 272.3	996.0 ± 191.2	1101.2 ± 263.9	**0.001**
Inhibin A level (pg/mL)	30.82 ± 4.2	136.4 ± 121.5	216.8 ± 146.1	**0.001**

Mention the statistical interpretation under the table and show the significant differences and at any probability level

**t* test was used DF= 12

P value > 0.05 not significant, *P*-value < 0.05 significant, *P* value < 0.01 highly significant

Table 2: Post hoc tests (LSD) to confirm the differences in mean of biomarkers between study groups

	Study group			*P* Value
	Complete Mean ± SD	Incomplete Mean ± SD	Control Mean ± SD	
B-hCG level (mIU/mL)	1446.2 ± 519.8	4626.3 ± 2601.0	-	**0.055**
	1446.2 ± 519.8	-	13301.2 ± 7623.1	**0.001**
	-	4626.3 ± 2601.0	13301.2 ± 7623.1	**0.001**
Activin A level (pg/mL)	720.4 ± 272.3	996.0 ± 191.2	-	**0.001**
	720.4 ± 272.3	-	1101.2 ± 263.9	**0.001**
	-	996.0 ± 191.2	1101.2 ± 263.9	**0.064**
Inhibin A level (pg/mL)	30.82 ± 4.2	136.4 ± 121.5	-	**0.005**
	30.82 ± 4.2	-	216.8 ± 146.1	**0.001**
	-	136.4 ± 121.5	216.8 ± 146.1	**0.001**

Mention the statistical interpretation under the table and show the significant differences and at any probability level

*t test was used DF= 12

P value > 0.05 not significant, P value < 0.05 significant, P value < 0.01 highly significant

Table 3: Diagnostic accuracy of biomarkers for risk of miscarriage

Marker	Cut-off value	Sensitivity	Specificity	PPV	NPV	Accuracy
β-hCG level (mIU/mL)	8750	95.7%	88.9%	89.8%	95.2%	92.3%
Activin A level (pg/mL)	822.0	78.3%	86.8%	66.7%	92.2%	84.6%
Inhibin A level (pg/mL)	104.81	88.2%	78.3%	92.3%	69.2%	85.7%

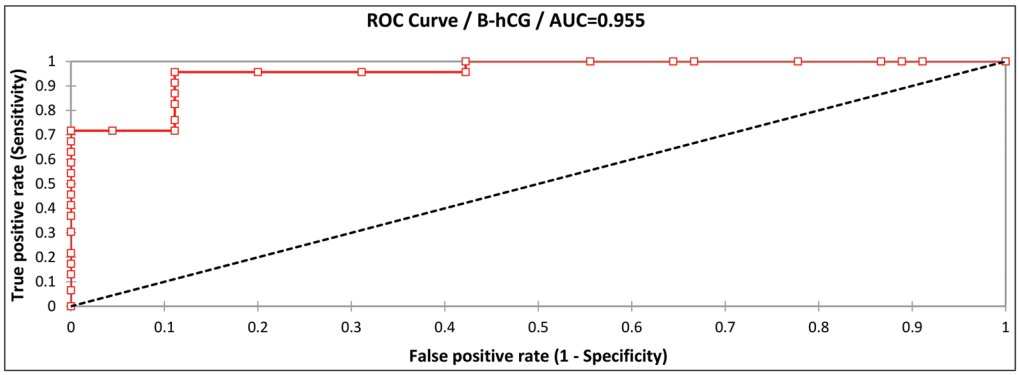

Figure 1: ROC curve for serum B-hCG marker as a predictor for risk of miscarriage

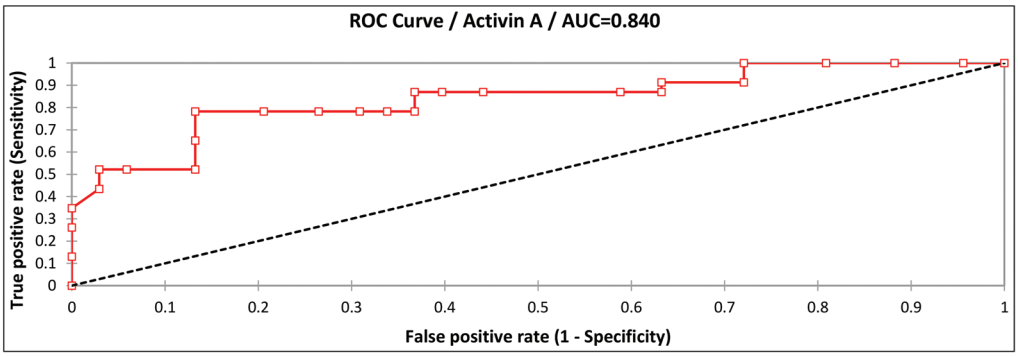

Figure 2: ROC curve for serum Activin A marker as a predictor for the occurrence of complete miscarriage

84.6% accurate, and inhibin A marker concentration was 88.2% sensitive, 78.3% specific, and 85.7% accurate as predictors for occurrence of complete miscarriage.

No significant difference was found among level activin, inhibin A level, and β-hCG level among the studied group the two groups regarding the gestational week for

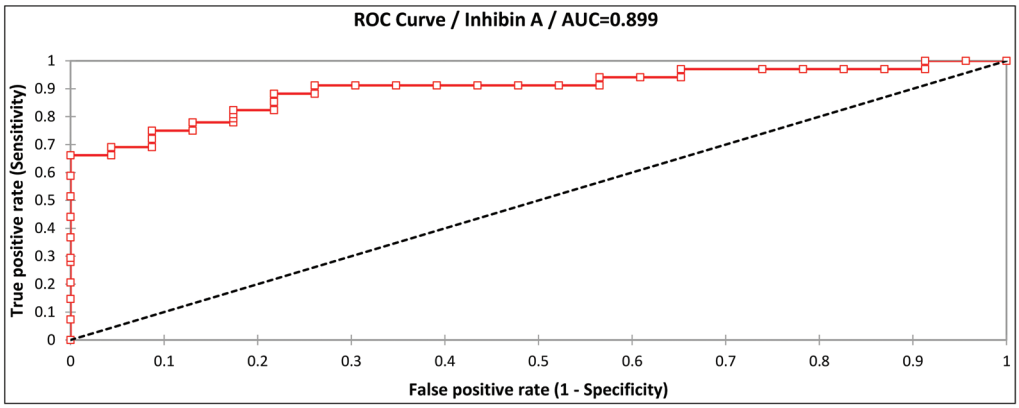

Figure 3: ROC curve for serum Inhibin A marker as a predictor for risk of miscarriage

Table 4: Comparison in the mean of biomarker levels between study groups according to the gestational age

Gestational age (week)	Complete Mean ± SD	Incomplete Mean ± SD	Control Mean ± SD	*P*-value
β-hCG Level (mIU/mL)				
5–8^{+6}	1415.0±474.7	4558.9±2749.1	13563.8±8138.3	**0.001**
9–12	1462.8±630.0	4699.7±2561.0	15425.7±6815.1	**0.001**
Activin A (pg/mL)				
5–8^{+6}	772.5±237.9	991.8±202.2	1068.3±246.8	**0.001**
9–12	849.9±298.6	999.7±178.7	1160.8±291.1	**0.026**
Inhibin A (pg/mL)				
5–8^{+6}	30.0±4.3	130.0±111.9	191.0±91.6	**0.001**
9–12	31.5±4.3	147.7±145.5	240.4±183.9	**0.001**

Mention the statistical interpretation under the table and show the significant differences and at any probability level

t test was used DF= 10

P value > 0.05 not significant, *P* value < 0.05 significant, *P* value < 0.01 highly significant

gestational week, there was no statistically significant relationship found among the level A activin, inhibin A level, and β-hCG level between the complete and incomplete groups with *P* value = 0.001.

As shown in Table 4, mean of β-hCG, activin A, and inhibin A levels were significantly lower ($P < 0.05$) in complete group than that in other groups both in early and late 1st trimester miscarriage periods.

Discussion

Many women experience pregnancy loss, and bleeding is the most common reason for seeking medical advice early in pregnancy. In fact, women seek medical care at various stages of miscarriage, sometimes after the miscarriage has already occurred, and sometimes before it has even begun, but even though miscarriage is common, it can be emotionally challenging. Although ultrasound is the best diagnostic test, its role as a prognostic test is not yet proven. As a result, various hormones and biochemical markers have been studied to aid in predicting pregnancy outcome in the first trimester as well as the risk of future miscarriage, with varying degrees of success.[13] In the present study, means of β-hCG, activin A, and inhibin A levels were significantly lower in those with complete and incomplete miscarriage than that in controls. β-hCG < 8750 mIU/mL, activin A < 822 pg/mL, and inhibin A < 104.81 pg/mL were found to be predictive for the occurrence of complete miscarriage. Agreement observed in studies conducted by Mansy *et al.*[14] and Luisi *et al.*[15] regarding β-hCG level, Daptone *et al.*[16] regarding activin A level, and Abd El Hameed *et al.*,[17] Prakash *et al.*,[18] and AL-Azemi *et al.*[19] regarding inhibin A level. β-hCG promotes the invasion process during pregnancy implantation and is a key angiogenic element for the fetomaternal unit, in addition to its invasion stimulating impact. Low HCG production during implantation is predicted to result in incorrect implantation and loss.[16] Activin A secretion is dynamic throughout pregnancy, since it is down and up regulated during the decudulization process, and serum levels are up to 69 times higher in pregnant women than non-pregnant women, with levels increasing throughout pregnancy.[20] The production and excretion of activin A from sources other than fetoplacental units, such as the corpus luteum and decedualized endometrium, peripheral mono nuclear cells, vascular endothelial cells, and bone

marrow, may account for our findings of non-significant reduction in activin A between control and incomplete.[21] As a result, early in the miscarriage process, the placental concentration of Activin A may not be entirely reflected in the circulating concentration; however, as the miscarriage progressed and completed, the expulsion of all trophoblasts as well as the shedding of the endometrium occurred, and the activin A level significantly dropped.[22] Inhibins have been investigated for a long time and are thought to play a role in reproductive physiology. Although their primary purpose is to limit gonadotropin secretion via negative feedback, they may also play a role in pregnancy by promoting and modulating placental secretary activity as well as placental immunological regulation.[23] In conclusion, Inhibin A level was comparably sensitive and less specific than B-hCG in predicting early miscarriage, this suggest a possible role of inhibin A in signaling early pregnancy problems especially if combined with B-hCG. Inhibin A has a shorter half-life than B-hCG making it superior to the later hormone in predicting the remnant of viable trophoblastic tissue and differentiation between complete and incomplete miscarriage. Activin A level is not helpful in predicting early pregnancy outcome but considered as promising biomarker in combination with inhibin A in determining the reminisce of viable from non-viable trophoblastic tissue.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Kanmaz AG, Inan AH, Beyan E, Budak A. The effects of threatened abortions on pregnancy outcomes. Ginekol Pol 2019;90:195-200.
2. Fawzi RQ, Rifat AG. The evaluation of maternal serum glycodelin level as a marker for the presence and severity of preeclampsia. Med J Babylon 2023;20(Suppl_1):S95-100.
3. Sakran SM, Ghazi HF, Khazaali EA. Programmed death receptor 1 gene polymorphisms influence the occurrence of recurrent pregnancy loss among Iraqi women. Med J Babylon 2025;22(Suppl_1): S122-7.
4. Wyatt PR, Owolabi T, Meier C, Huang T. Age-specific risk of fetal loss observed in a second trimester serum screening population. Am J Obstet Gynecol 2005;192:240-6.
5. Weghofer A, Barad DH, Darmon SK, Kushnir VA, Albertini DF, Gleicher N. Euploid miscarriage is associated with elevated serum C-reactive protein levels in infertile women: A pilot study. Arch Gynecol Obstet 2020;301:831-6.
6. Lyall F, Robson SC, Bulmer JN. Spiral artery remodeling and trophoblast invasion in preeclampsia and fetal growth restriction: Relationship to clinical outcome. Hypertension 2013;62:1046-54.
7. Jauniaux E, Burton G. Pathophysiology of histological changes in early pregnancy loss. Placenta 2005;26:114-23.
8. Yue C-Y, Zhang C-Y, Ni Y-H, Ying C-M. Are serum levels of inhibin A in second trimester predictors of adverse pregnancy outcome? PLoS One 2020;15:e0232634.
9. Yu J, Shixia C, Wu Y, Duan T. Inhibin A, activin A, placental growth factor and uterine artery Doppler pulsatility index in the prediction of pre-eclampsia. Ultrasound Obstetr Gynecol 2011;37:528-33.
10. Esraa Hameed Humadi A-M, Israa Tailb Abd A-K, Rawnaq Ali A-S. The role of activin a and follistatin in the differentiation between viable intrauterine pregnancy from missed miscarriage and ectopic pregnancy. Asian J Pharm Clin Res 2019;12:197-202.
11. Hauzman E, Fedorcsák P, Klinga K, Papp Z, Rabe T, Strowitzki T, *et al*. Use of serum inhibin A and human chorionic gonadotropin measurements to predict the outcome of in vitro fertilization pregnancies. Fertil Steril 2004;81:66-72.
12. BBS. The Pocket Book of Statistics. Dhaka, Bangladesh: Bangladesh Bureau of Statistics (BBS); 2009.
13. Jayasena C, Abbara A, Izzi-Engbeaya C, Comninos A, Harvey R, Gonzalez Maffe J, *et al*. Reduced levels of plasma kisspeptin during the antenatal booking visit are associated with increased risk of miscarriage. J Clin Endocrinol Metab 2014;99:E2652-E60.
14. Mansy AA, Taher E, Abdelrahman M, Shehata SM. CA125, progesterone & β-hCG in prediction of first trimester abortion. Reprodução Climatério 2017;32:24-30.
15. Luisi S, Florio P, Antona D D, Severi F, Sanseverino F, Danero S, *et al*. Maternal serum inhibin A levels are a marker of a viable trophoblast in incomplete and complete miscarriage. Eur J Endocrinol 2003;148:233-6.
16. Daponte A, Deligeoroglou E, Garas A, Pournaras S, Hadjichristodoulou C, Messinis IE. Activin A and follistatin as biomarkers for ectopic pregnancy and missed abortion. Dis Markers 2013;35:497-503.
17. Abd El Hameed AA, Hasan MM. Maternal serum β-HCG, progesterone, activin a, inhibin a and uterine artery blood flow as predictors of the outcome of threatened abortion. Al-Azhar Assiut Med J 2015;13:1.
18. Prakash A, Laird S, Tuckerman E, Li TC, Ledger WL. Inhibin A and activin A may be used to predict pregnancy outcome in women with recurrent miscarriage. Fertil Steril 2005;83:1758-63.
19. Al-Azemi M, Ledger WL, Diejomaoh M, Mousa M, Makhseed M, Omu A. Measurement of inhibin A and inhibin pro-αC in early human pregnancy and their role in the prediction of pregnancy outcome in patients with recurrent pregnancy loss. Fertil Steril 2003;80:1473-9.
20. Florio P, Luisi S, Ciarmela P, Severi F, Bocchi C, Petraglia F. Inhibins and activins in pregnancy. Mol Cell Endocrinol 2004;225:93-100.
21. Muttukrishna S, North R, Morris J, Schellenberg J-C, Taylor R, Asselin J, *et al*. Serum inhibin A and activin A are elevated prior to the onset of pre-eclampsia. Hum Reprod 2000;16:200-200.
22. Muttukrishna S, Jauniaux E, Greenwold N, McGarrigle H, Jivraj S, Carter S, *et al*. Circulating levels of inhibin A, activin A and follistatin in missed and recurrent miscarriages. Hum Reprod 2002;17:3072-8.
23. Namwanje M, Brown CW. Activins and inhibins: Roles in development, physiology, and disease. Cold Spring Harb Perspect Biol 2016;8:a021881.